·青年编委专栏·

信号转导和转录激活因子3在牙发育中的机制研究进展

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【摘要】 牙发育是一个复杂且精确的过程,涉及上皮和外胚间充质之间的相互作用,多个信号通路和调节因子参与其中。正常的牙发育对于个体的发音、咀嚼功能和颅颌面部的整体发育至关重要。信号转导与转录激活因子3(STAT3)是一种关键的转录因子,参与细胞增殖、存活、凋亡、血管生成、免疫反应和细胞迁移等过程。研究表明,STAT3在牙发育过程中可能扮演着重要角色。本文回顾了近年来关于*STAT3*在牙发育中的研究进展,重点讨论了STAT3在成釉细胞、成牙本质细胞、牙髓干细胞和成牙骨质细胞分化中的作用,以期为临床牙发育异常的诊断和治疗提供新的思路和参考。

【关键词】 牙发育异常; 信号转导和转录激活因子3; 成釉细胞; 成牙本质细胞; 成牙骨质细胞

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New advances of the mechanism of signal transducer and activator of transcription 3 in tooth development

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【Abstract】 Tooth development is a complex and precise process involving interactions between epithelial and ectomesenchymal tissues, with multiple signaling pathways and regulatory factors participating. Proper tooth development is crucial for phonation, mastication, and the overall development of the craniofacial region. Signal transducer and activator of transcription 3 (STAT3), a key transcription factor, plays a critical role in processes such as cell proliferation, survival, apoptosis, angiogenesis, immune responses, and cell migration. Recent studies have highlighted the significant role of STAT3 in tooth development. This paper summarizes recent advancements in the research on STAT3 in tooth development, with a focus on its role in ameloblasts, odontoblasts, dental pulp stem cells, and cementoblast differentiation, so as to offer new perspectives and references for the diagnosis and treatment of clinical tooth development abnormalities.

【Key words】 Tooth dysplasia; Signal transducer and activator of transcription 3; Ameloblast; Odontoblasts; Cementoblast

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牙及其支持组织的发育是一个高度复杂且精细的过程,起源于胚胎期的上下颌突及额鼻突的外胚层和外胚间充质。这一过程不仅涉及上皮与间充质之间的相互作用,还需要多个信号通路和调节因子的精确调控,如音猬因子(sonic hedgehog,SHH)信号通路、Wnt信号通路、成纤维细胞生长因子(fibroblast growth factor,FGF)信号通路和转化生长因子β(transforming growth factor-β,TGF-β)信号通路等。牙及其支持组织的正常发育对于个体的发音、咀嚼功能乃至颅颌面部的发育都有着至关重要的作用,进而影响个体的全身健康和社会心理健康[1]。信号转导和转录激活因子3(signal transducer and activator of transcription 3,STAT3)作为一种转录因子,参与并调控多种细胞过程,包括正常发育和免疫功能期间的细胞增殖、存活和分化,以及肿瘤的生长、侵袭和转移[2]。系统性敲除*Stat3*基因的小鼠在胚胎发育约7 d时死亡,表明*Stat3*基因的纯合突变

具有胚胎致死性[3]。STAT3显性负突变会导致高IgE综合征(hyper immunoglobulin-E syndrome, HIES),患者大多数都有相关的颅颌面畸形,在口腔方面症状主要表现为乳牙滞留、恒牙迟萌、复发性口腔念珠菌感染、龋齿、上腭和舌背病变等,预示着STAT3可能在牙发育过程中扮演着举足轻重的角色[4-5]。本文回顾了近年来STAT3在牙发育中的研究报道,重点阐述了STAT3在成釉细胞、成牙本质细胞、牙髓干细胞和成牙骨质细胞分化中的作用,以期为临床牙发育异常的诊断与治疗提供新的思路与参考。

一、信号转导和转录激活因子3的结构与功能

STAT具有传递胞浆信号和启动细胞核内基因转录的双重功能,是介导细胞信号转导的重要胞内转录因子家族,包括STAT1、STAT2、STAT3、STAT4、STAT5a、STAT5b和STAT6[6]。其中,人类*STAT3*基因位于染色体17q21上,编码蛋白相对分子质量为89 000,具有STAT3α、STAT3β、STAT3γ和STAT3δ 4种异构体[7]。STAT3主要由6个结构域构成,包括氨基末端结构域、DNA结合结构域、SH2结构域、反式激活结构域、coiled-coil结构域和linker结构域。在信号传导和基因转录激活过程中,每个结构域都各自发挥着不同的作用。氨基末端结构域参与STAT3二聚体核转位、协同DNA结合和蛋白质-蛋白质相互作用形成各种二聚体复合物以及随后的负调控过程[8];DNA结合结构域可识别特定的DNA序列,并在蛋白质和DNA之间提供结合界面以形成STAT3-DNA复合体[9];SH2结构域参与STAT3与激酶受体残基的结合和二聚化[10]。此外,STAT3的激活与酪氨酸705(Tyrosine 705, Tyr705)和丝氨酸727(Serine 727, Ser727)的磷酸化密切相关[11]。在正常细胞中,STAT3通过磷酸化瞬时激活,将质膜上的细胞因子和生长因子受体的信号传递到细胞核。然而,在多种肿瘤细胞中,STAT3被持续性激活并呈高水平表达,参与调控一系列与癌细胞生存、增殖、血管生成、侵袭、转移、耐药性和免疫逃逸相关的基因[6]。

二、信号转导和转录激活因子3参与调节牙的生长发育

HIES是一组罕见的原发性免疫缺陷病,其主要致病基因是*STAT3*。该病于1966年由Davis等[12]首次报道。HIES可呈现常染色体显性或隐性遗传模式,且由多个致病基因突变引起。其中,*STAT3*基因的显性突变导致的常染色体显性遗传HIES,已被确认为经典HIES的主要分子病因[4]。HIES患者常伴有颅颌面畸形,特别是在口腔方面,表现为乳牙滞留和恒牙迟萌、复发性口腔念珠菌感染、广泛性龋齿及上腭和舌背病变等症状[5]。研究发现,STAT3在牙发育过程中扮演着重要角色。在牙胚形成初期,*Stat3*在口腔上皮细胞中高度表达[13];在牙发育中期,STAT3参与牙釉质与牙本质的矿化,在成釉细胞与成牙本质中表达[14]。已有研究证明,STAT3可能通过调节骨桥蛋白参与牙发育的调控[15]。进一步研究中,Chan等[16]发现*Stat3*缺失小鼠门牙牙釉质明显缺损,磨牙牙本质变薄,髓室体积显著增大,牙根变短。该研究表明,*Osterix*(+)细胞中的*Stat3*在牙发育的上皮-间充质相互作用中起着重要作用;*Stat3*缺失会导致β-catenin表达降低,提示*Stat3*可能通过β-cantenin信号通路来调节细胞增殖分化,进而影响牙本质及牙根的发育。综上所述,STAT3功能失调会导致牙发育过程中的结构和功能异常,本文将从STAT3在成釉细胞、成牙本质细胞、牙髓干细胞和成牙骨质细胞的作用机制阐述STAT3与牙发育的关系。

1. STAT3可促进成釉细胞和成牙本质细胞的分化,参与牙釉质和牙本质的形成:成釉细胞起源于内釉上皮细胞,主要功能是分泌釉质基质,是牙釉质形成的基础[17]。牙本质是牙齿的主体矿化组织,具有支撑牙釉质、保护牙髓等重要功能,在牙发育过程中牙本质的生成占重要地位[18]。有学者对人类胎儿牙胚包埋切片,进行免疫组化分析后发现,STAT3可促进成釉细胞和成牙本质细胞的分化[14]。后又有研究发现,*Stat3*可直接在大鼠臼齿牙本质和牙釉质形成的细胞中表达[19]。Fan等[20]发现,相较于野生型小鼠,白血病抑制因子(leukaemia inhibitory factor, LIF)缺陷小鼠门牙颜色更白、长度更短、硬度与耐酸性更低;LIF在牙釉质发育过程中,可通过*Stat3*信号通路调节转铁蛋白受体基因(transferrin receptor gene, *Tfrc*)和溶质载体家族40(铁调控转运蛋白),成员1[(solute carrier family 40 (iron-regulated transporter), member 1, Slc40a1]的表达,从而调控成釉细胞中的铁转运。Zhang等[13]发现,*Stat3*可在幼年和成年小鼠牙齿的上皮细胞中表达,当*Stat3*缺失时,小鼠门牙牙釉质延迟矿化。Sarper等[21]则证明了,*Stat3*可通过调节颈环中的Runx1-Lgr5轴,使牙釉质基质蛋白显著下降,上皮细胞中缺乏Runx1的小鼠则表现出明显的门牙缩短,颈袢发育不全和牙釉质缺损。综上所述,STAT3可

促进成釉细胞和成牙本质细胞的分化,参与牙釉质与牙本质的形成。

2. STAT3促进牙髓干细胞分化,维持牙髓干细胞多能性:牙髓干细胞可分化为成牙本质细胞和血管内皮细胞,形成新生牙本质、血管及神经,促进牙髓活力恢复及牙根的继续发育[22]。成牙本质细胞分泌的蛋白质、基质和生长因子等在牙本质形成、矿化等过程中发挥着重要作用。研究发现,MiR-21的下调会抑制STAT3的激活,从而减少成牙本质细胞分化的标志蛋白的表达,表明MiR-21/STAT3信号可能在复杂的因子网络中充当调节剂,以调节人类牙髓干细胞的成牙本质细胞分化[23]。此外,硬化蛋白的表达下调也可通过STAT3信号通路促进人牙髓来源的成牙本质细胞分化[24]。Zhou等[25]也发现LIF和白血病抑制因子受体(leukemia inhibitory factor receptor,LIFR)均在人牙髓中表达。LIF可促进牙髓细胞的增殖,并通过JAK2/STAT3信号通路抑制成牙本质细胞的分化。所以,STAT3信号通路的激活能促进牙髓干细胞向成牙本质细胞分化,牙本质基质分泌增多,从而促进牙本质的生成与矿化。Peng等[26]发现,STAT3可直接与*POU5F1*(以前被称为*OCT-4*)和*SOX2*基因启动子区域结合并激活这些基因的表达,在调节牙髓细胞和牙周韧带细胞(periodontal ligament cell,PDLC)的多能性方面发挥重要作用。也有研究发现,内皮细胞来源的IL-6可通过STAT3信号传导和Bmi-1的诱导增强牙髓干细胞的自我更新[27]。2,3,5,4′-四羟基二苯乙烯-2-O-β-葡萄糖苷(2,3,5,4′-tetrahydroxystilbene-2-O-β-glucoside,THSG)也可通过JAK2/STAT3信号通路提高牙髓干细胞的多能性[28]。

三、信号转导和转录激活因子3参与调节牙周组织的生长发育

牙周组织是支持并包绕在牙齿周围的组织,包括牙骨质、牙周膜和固有牙槽骨,均由牙囊发育而来,并随着牙根的形成而发育[29]。研究表明,STAT3可参与牙周组织的生长发育并维持牙周组织的稳态。

1. STAT3可促进成牙骨质细胞分化,调节牙周组织发育:成牙骨质细胞可合成和分泌牙骨质基质,矿化后形成坚硬的牙骨质,从而维持牙周组织的稳定性和完整性。肿瘤坏死因子α(tumor necrosis factor-α,TNF-α)在成牙骨质细胞分化、矿化和细胞凋亡中起着重要作用。研究表明,TNF-α可能通过*STAT3*信号通路影响成牙骨质细胞的自噬作用[30]。此外,研究发现在成牙骨质细胞中,睫状神经营养因子(ciliary neurotrophic factor,CNTF)可通过激活STAT3/ERK信号传导减少骨保护素(osteoprotegerin,OPG)的表达,从而使成牙骨质细胞的矿化能力降低[31]。Yang等[32]也发现,脂联素能诱导丝裂原激活蛋白激酶8(mitogen-activated protein kinase 8,MAPK8)、P38、细胞外调节蛋白激酶1和2(extracellular signal-regulated kinase 1 and 2,ERK1/2)的瞬时激活并促进STAT1和STAT3的磷酸化,部分通过MAPK信号通路促进成牙骨质细胞迁移、增殖和牙骨质的形成。综上所述,STAT3信号通路可能参与调控成牙骨质细胞的分化、增殖和功能活动。

2. STAT3维持牙周稳态:牙周病是一种常见的慢性炎症性疾病,其发病机制复杂且多样,核心致病因素通常归因于牙菌斑中的微生物群落。然而,疾病进展的主要驱动因素是机体对微生物的免疫损伤反应[33]。STAT3是与牙周病进展息息相关的重要转录因子之一。研究发现,在牙周病患者的牙周韧带成纤维细胞中,STAT3被显著激活并表达上调[34]。牙龈卟啉单胞菌(*Porphyromonas gingivalis*,Pg)是牙周炎最主要的致病微生物,可与宿主免疫防御系统相互作用,激活一系列炎症反应,从而诱导小鼠巨噬细胞中各类细胞因子的表达,最终导致小鼠骨质流失[35]。有研究表明,磷酸化的STAT3参与介导了Pg诱导的巨噬细胞极化,而抑制STAT3通路能有效缓解由于感染Pg所诱导的骨吸收[36-37]。此外,激活上皮细胞和T细胞的*STAT3*可诱导牙槽骨炎性骨质丧失,表明STAT3可能在牙周炎的炎性组织破坏中发挥作用[38]。值得注意的是,牙周病多个危险因素如吸烟和糖尿病等均会激活STAT3,进而促进持续性的炎症反应[39-40]。

四、总结

牙及其支持组织的发育由上皮和外胚间充质的相互作用驱动,其正常发育对个体的发音、咀嚼功能及颌面部的健康至关重要。STAT3是一种在细胞因子和生长因子刺激下激活的关键转录因子,它不仅介导了各种白细胞介素的信号通路,还在免疫反应、炎症以及细胞生长和凋亡等多个生物过程中发挥关键作用。同时,STAT3通过促进成釉细胞、成牙本质细胞、牙髓干细胞和成牙骨质细胞的分化,参与调节牙及其支持组织的生长发育,并维持牙周组织的稳态。因此,深入研究STAT3在牙齿正常发

育中的遗传与分子机制具有重要意义。这不仅有助于对牙发育异常的患者开发针对性的治疗和健康管理策略,还能为改善因STAT3功能异常导致的牙发育异常提供新的诊断和治疗靶点。

利益冲突 所有作者均声明不存在利益冲突

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